**Dioxin**

## Reproductive Studies in Animals on the Effects of Dioxin and/or Similar Chemicals

**1)** J Immunotoxicol. 2009 Mar;6(1):74.

### Perinatal TCDD exposure and the adult onset of autoimmune disease.

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**Abstract:** Modulation of the developing immune system can occur following perinatal exposure to a number of immunotoxic compounds, including polyhalogenated hydrocarbons like 2,3,7,8-tetra-chlorodibenzo-p-dioxin (TCDD; dioxin), the most toxic of the congeners. T hese data suggest that gestational exposure to TCDD may interfere with normal development of central tolerance in the thymus. In possible support of this theory, when autoimmune disease-prone mice were treated with TCDD during gestation, postnatal autoimmunity had an accelerated onset and was exacerbated. This review provides an overview of the currently available information, which appears to support a hypothesis for increased risk of postnatal autoimmune responses as a result of TCDD exposure during the sensitive time of immune system establishment.

**2)** J Pharmacol Exp Ther. 2009 Jun;329(3):1091-9. Epub 2009 Mar 10.

**Maternal exposure to dioxin disrupts gonadotropin production in fetal rats and imprints defects in sexual behavior.**

Takeda T, Matsumoto Y, Koga T, Mutoh J, Nishimura Y, Shimazoe T, Ishii Y, Ishida T, Yamada H.Graduate School of Pharmaceutical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.

**Abstract:** 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and related substances are a class of environmental pollutants with suspected toxic effects on reproductive and developmental processes. Maternal exposure to TCDD delayed the development of gonadal tissues in male and female pups and impaired their sexual behavior.

3) Toxicol Appl Pharmacol. 2008 Dec 15;233(3):454-8. Epub 2008 Sep 24.

Lymphoma and lung cancer in offspring born to pregnant mice dosed with dibenzo[a,l]pyrene: the importance of in utero vs. lactational exposure.

Castro DJ, Löhr CV, Fischer KA, Pereira CB, Williams DE.

Department of Environmental and Molecular Toxicology, Oregon State University, Corvallis, OR 97331-7301, USA.

**Abstract:** Animal models demonstrate that environmental chemicals, to which pregnant women are daily exposed, can increase susceptibility of the offspring to cancer. We developed a pregnant mouse model in which exposure to the polycyclic aromatic hydrocarbon (PAH), dibenzo[a,l]pyrene (DBP), during late gestation, produces an aggressive T-cell lymphoma in offspring between 3 and 6 months of age. Survivors exhibit multiple lung and liver (males) tumors.

4) Toxicology. 2008 Nov 20;253(1-3):147-52. Epub 2008 Sep 12.

In utero and lactational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) affects bone tissue in rhesus monkeys.

Hermsen SA, Larsson S, Arima A, Muneoka A, Ihara T, Sumida H, Fukusato T, Kubota S, Yasuda M, Lind PM.

Institute of Environmental Medicine, Karolinska Institutet, Nobels väg 13, Box 210, S-17177 Stockholm, Sweden.

**Abstract:** Bone tissue is one of the target tissues for dioxins and dioxin-like compounds… In conclusion, in utero and lactational low-dose, but not high-dose exposure to 2,3,7,8-TCDD induced disruption of bone tissue development in rhesus monkey, a result suggesting that similar effects might occur in humans also.

5) Cardiovasc Toxicol. 2008 Fall;8(3):145-54. Epub 2008 Aug 1.

**Perinatal 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure sensitizes offspring to angiotensin II-induced hypertension.**

Aragon AC, Goens MB, Carbett E, Walker MK.College of Pharmacy, University of New Mexico, MSC09 5360, 2703 Frontier Ave, Suite 220, Albuquerque, NM, 87131-5691, USA.

**Abstract:** In utero and lactational exposure of mice to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) leads to cardiac hypertrophy and hydronephrosis in adulthood.

**6)** Toxicol Pathol. 2008;36(5):705-13. Epub 2008 Jul 22.

Mid-gestation exposure of C57BL/6 mice to 2,3,7,8-tetrachlorodibenzo-p-dioxin causes postnatal morphologic changes in the spleen and liver.

Weinstein DA, Gogal RM Jr, Mustafa A, Prater MR, Holladay SD.Department of Biomedical Sciences and Pathobiology, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, Blacksburg, Virginia 24601-0442, USA. dweinste@vt.edu

**Abstract:** These results suggest that late-gestation thymic architectural changes caused by TCDD resolve shortly after birth: however, abnormalities in other immunologically important areas may appear later in postnatal life.

**7)** Toxicol Appl Pharmacol. 2008 Oct 1;232(1):51-9. Epub 2008 Apr 30.

**An enhanced postnatal autoimmune profile in 24 week-old C57BL/6 mice developmentally exposed to TCDD.**

Mustafa A, Holladay SD, Goff M, Witonsky SG, Kerr R, Reilly CM, Sponenberg DP, Gogal RM Jr.Center for Molecular Medicine and Infectious Diseases, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061-0342, USA.

**Abstract:** These results show that exposure to TCDD during immune system development causes persistent humoral immune dysregulation as well as altered cell-mediated responses, and induces an adult profile of changes suggestive of increased risk for autoimmune disease.

**8)** Toxicol Lett. 2007 Aug 30;173(1):41-7. Epub 2007 Jun 20.

**Effects of maternal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin on fetal brain growth and motor and behavioral development in offspring rats.**

Nishijo M, Kuriwaki J, Hori E, Tawara K, Nakagawa H, Nishijo H.Department of Public Health, Kanazawa Medical University, 1-1 Daigaku, Uchinada, Ishikawa, Japan. ni-koei@kanazawa-med.ac.jp

**Abstract:** The results demonstrated that maternal TCDD exposure delayed fetal brain growth and neurodevelopment of the offspring in early stage, especially in male rats.

**9)** Toxicol Appl Pharmacol. 2007 Oct 1;224(1):29-38. Epub 2007 Jun 26.

**Gestational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin alters retinoid homeostasis in maternal and perinatal tissues of the Holtzman rat.**

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**Abstract:** 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), one of the most widely studied environmental contaminants, causes a variety of adverse health effects including teratogenesis and altered development which may be related to disruptions in retinoid homeostasis . These data demonstrate that TCDD significantly alters retinoid homeostasis in tissues of the developing fetus and neonate, suggesting that their unique sensitivity to TCDD may at least be in part the result of altered retinoid homeostasis.

**10)** Life Sci. 2007 Mar 13;80(14):1259-67. Epub 2007 Jan 18.

**Suppression of fetal testicular cytochrome P450 17 by maternal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin: a mechanism**

**involving an initial effect on gonadotropin synthesis in the pituitary.**

Taketoh J, Mutoh J, Takeda T, Ogishima T, Takeda S, Ishii Y, Ishida T, Yamada H.

Graduate School of Pharmaceutical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.

**Abstract:** These results suggest that 1) maternal exposure to TCDD impairs the expression of testicular CYP17 in a fetal stage-specific manner; 2) this effect is due, at least partially, to a TCDD-produced reduction in circulating LH (pituitary luteinizing hormone); and 3) TCDD exerts such an effect by affecting the upstream mechanism regulating the pituitary synthesis of LH.

11) Reprod Toxicol. 2007 Apr-May;23(3):391-6. Epub 2006 Nov 10.

**Prenatal TCDD exposure predisposes for mammary cancer in rats.**

Jenkins S, Rowell C, Wang J, Lamartiniere CA.Department of Pharmacology and Toxicology, University of Alabama at Birmingham, Birmingham, AL, USA. Jenkinss@uab.edu

**Abstract:** Epidemiological data are conflicting in the link between 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure and breast cancer causation. We have hypothesized that timing of exposure to endocrine disruptors, such as TCDD, will alter breast cancer susceptibility. We conclude that prenatal TCDD can predispose for mammary cancer susceptibility in the adult offspring by altering the mammary proteome.

**12)** Arch Oral Biol. 2007 May;52(5):450-4. Epub 2006 Dec 4.

Qualitative effects of dioxin on molars vary among inbred mouse strains.

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**Abstract:** We evaluated the effects of different levels of the potent environmental toxicant and teratogen, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), on molar development in mice in six inbred strains, all with TCDD responsive Ahr alleles. Inbred mice strains exhibited differential responses to TCDD suggesting that there is a genetic component, beyond Ahr differences, mediating the effects of TCDD on molar development.

13) Neurotoxicology. 2006 Dec;27(6):1032-42. Epub 2006 Jun 7.

Gestational 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure effects on sensory cortex function.

Hood DB, Woods L, Brown L, Johnson S, Ebner FF.Department of Biomedical Sciences, Division of Neurobiology and Neurotoxicology, Center for Molecular and Behavioral Neuroscience, Meharry Medical College, Nashville, TN 37208, USA.

**Abstract:** Gestational exposure to environmental contaminants such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) poses a significant threat to normal growth and differentiation of the developing brain. The results indicate that gestational TCDD exposure results in cortical deficits that are paralled by diminished expression of certain NMDA and AMPA receptor subunits at a time when synapses are being formed for the first time in cortex.

14) The effect of perinatal TCDD exposure on caries susceptibility in rats.

Toxicol Sci. 2006 Jun;91(2):568-75. Epub 2006 Mar 16.

Miettinen HM, Sorvari R, Alaluusua S, Murtomaa M, Tuukkanen J, Viluksela M.Laboratory of Toxicology, Department of Environmental Health, National Public Health Institute, Kuopio, Finland. hanna.miettinen@ktl.fi

**Abstract:** 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), the model compound of polychlorinated dibenzo-p-dioxins and furans, is a potent toxicant with the ability to hamper development. Accidental exposure to TCDD has been linked with various developmental dental aberrations in humans, and experimentally it has been shown that TCDD causes, among other defects, hypomineralization of dental hard tissues in rodents. In conclusion, perinatal TCDD exposure can render rat molars more susceptible to caries.

15) Sex-specific alterations of cerebral cortical cell size in rats exposed prenatally to dioxin.

J Appl Toxicol. 2006 Jan-Feb;26(1):25-34.

Hojo R, Zareba G, Kai JW, Baggs RB, Weiss B.Department of Environmental Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York 14642, USA.

**Abstract:** Sex-specific patterns of cerebral cortical lateralization have been documented consistently in both the human and animal brain. Male rats tend to exhibit pronounced right hemisphere dominance compared with females, while females typically exhibit more diffuse lateralization patterns and greater left hemisphere bias compared with males. Prenatal TCDD (2,3,7,8 tetrachlorodibenzo-

p-dioxin) exposure produces demasculinization of male offspring sexual behavior, suggesting interference with sexual differentiation of the brain. Prenatal TCDD exposure altered the relative proportions of smaller and larger cell sizes in male, but not in female offspring. Both exposed males and females, however, exhibited a significant reversal of hemispheric dominance based on cell number. These findings demonstrate that prenatal exposure to TCDD alters the normal patterns of cortical cell asymmetry in a manner consistent with our previous data on thickness patterns.

16) Toxicol Appl Pharmacol. 2005 May 15;205(1):98-105.

In utero and lactational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats disrupts brain sexual differentiation.

Ikeda M, Mitsui T, Setani K, Tamura M, Kakeyama M, Sone H, Tohyama C, Tomita T.University of Shizuoka, Graduate School of Nutritional and Environmental Sciences, Japan. ikedam@ys2.u-shizuoka-ken.ac.jp

**Abstract:** The effects of in utero and lactational exposure of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on brain sexual differentiation were investigated. These results suggest that in utero and lactational TCDD exposure dose-dependently induces demasculinization in male offspring by inhibiting brain aromatase activity in the hypothalamus-preoptic area during central nervous system development.

17) Fukuoka Igaku Zasshi. 2003 May;94(5):183-95.

**[Effects of dioxins on the reproduction and development in mammals and the mechanism: up-to-date progress of study]**

[Article in Japanese]

Ishida T, Masuzaki Y, Nishimura Y, Yamada H.Graduate School of Pharmaceutical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582.

**Abstract:** In the Seveso episode, increase of female offspring from the parents exposed with dioxins has been demonstrated, although the same has not been seen in Yusho and Yu-cheng patients. However, delay of cognitive development in the children born from Yu-cheng patients has been reported. This has been recently supported by animal studies in which acquirement of cognitive capacity such as working memory and social behavior was examined in rats and monkeys treated in utero with dioxins. In this review, we summarize the prenatal and postnatal effects of dioxins on reproduction and development. In addition, dioxin-induced alteration of gene expression and of the function of estrogen-estrogen receptor system which may play a role in dioxin toxicity is discussed.

18) Environ Health Perspect. 2003 Apr;111(4):389-94.

## Cancer and developmental exposure to endocrine disruptors.

Birnbaum LS, Fenton SE.Experimental Toxicology Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA. birnbaum.linda@epa.gov

**Abstract:** Recently, a prototypical endocrine-disrupting compound, 2,3,7,8-tetrachlorodibenzo-p-dioxin, has been shown to be a developmental toxicant of the mammary gland in rodents. Dioxin alters multiple endocrine systems, and its effects on the developing breast involve delayed proliferation and differentiation of the

mammary gland, as well as an elongation of the window of sensitivity to potential carcinogens. Implications of these new findings suggest that causes of endocrine-related cancers or susceptibility to cancer may be a result of developmental exposures rather than exposures existing at or near the time of tumor detection.

19) Food Addit Contam. 2000 Apr;17(4):275-88.

**Non-carcinogenic effects of TCDD in animals.**

Birnbaum LS, Tuomisto J.National Health and Environmental Effects Research Laboratory, United States Environmental Protection Agency, Research Triangle Park, NC 27711-2055, USA.

**Abstract:** Thus, effects (of TCDD) on the immune system, learning, and the developing reproductive system of multiple animals occur at body burdens which are close to those present in the background human population.

20) Toxicol Sci. 2000 Apr;54(2):424-30.

In utero and lactational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin alters postnatal development of seminal vesicle epithelium.

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2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) has been shown to alter male reproductive development of laboratory animals through in utero and lactational exposure. As a result of exposure, the accessory glands of the male reproductive tract, including the seminal vesicle, are decreased in size as determined by total weight

of the tissue. Analysis of seminal vesicle weights over time suggests that the changes may be transient. Administration of 1.0 microg/kg TCDD during gestation caused a significant decrease in seminal vesicle weights of offspring 8-11 months of age. We examined the effects of TCDD on seminal vesicles from rats exposed in utero and lactationally. Pregnant Long Evans rats were gavaged on gestation day 15 with 1.0 microg/kg TCDD in corn oil. Male pups were euthanized and necropsied on postnatal days (PND) 15, 25, 32, 49, 63, and 120. Seminal vesicles were weighed and then fixed in 10% neutral buffered formalin and processed for microscopic examination. Seminal vesicle weights were not significantly decreased until PND 32. Androgen receptor mRNA expression in PND 25 seminal vesicles was not different from control. In the present study, TCDD exposure decreased seminal vesicle epithelial branching and differentiation. Control epithelial cells had tall columnar morphology with relatively abundant cytoplasm, whereas TCDD-treated cells had rounded nuclei and less cytoplasm. In addition, immunolocalization of proliferating nuclear antigen was confined to undifferentiated basal epithelial cells of controls but was found in both basal and luminal cells of the treated seminal vesicle. Results indicate that the TCDD-induced impaired growth of the rat seminal vesicles is associated with a dramatic decrease in the development of the epithelium.